REMARKS

The Invention

The invention features a biomaterial linked to a pharmaceutically active compound by an amide or ester bond and methods of formation, precursors, and uses thereof. The amide and ester bonds of the present invention are α or β to a secondary amine or thioether, which increases the rate of hydrolysis compared to aliphatic esters or amides.

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Substitute Specification

As requested by the Examiner, a substitute specification including the amendments filed on August 6, 2002 is submitted herewith. No new matter has been added.

Support for the Amendments

New claim 42 finds support throughout the application, for example, page 89, line 15 – page 90, line 17.

The Office Action

Claims 5-39 and 41 are pending. Claims 5-39 stand rejected for anticipation or obviousness in view of Plate et al. (U.S. Patent No. 5,945,457; hereafter "Plate"). Claims 18, 23, and 29 stand further rejected for indefiniteness. Applicants note that claim 40 was cancelled and claim 41 was added in the reply filed on August 6, 2002, but these amendments were was not acknowledged in the Office Action mailed on September 26, 2002. A clean copy of the pending claims is included for the Examiner's convenience.

Rejections under 35 U.S.C. § 112, second paragraph

Claims 18, 23, and 29 are rejected for indefiniteness for reciting the phrase "derivative thereof." The term "derivative" is defined in the specification as follows:

> By "derivative" of an organic molecule is meant a compound having a portion of the organic molecule and having the same therapeutic activity as the organic molecule. The derivative may have one more functional groups that are not present in the pharmaceutically active organic molecule. Additionally, the derivative might not have one or more functional groups that are present in the pharmaceutically active organic molecule. (pg. 35, ll. 5-10)

Thus, a derivative of a compound differs from that compound by typically minor changes in the functional groups that do not affect the therapeutic activity of the compound. The term is also used in the art to denote compounds that have been modified, for example, to

increase solubility or stability in vivo. Applicants assert that, based on the definition provided, one skilled in the art would understand the meaning of the term "derivative," and the rejection for indefiniteness may be withdrawn.

Rejections under 35 U.S.C. § 102(e)

Claims 5-39 are rejected for anticipation by Plate. M.P.E.P. § 2131 states, "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." (citations omitted) Plate does not meet this standard.

Plate is directed to hemocompatible polymeric compositions having a pharmacologic material covalently bound or grafted to a polymer. The pharmacologic material is preferably bonded to the polymer by reacting the pharmacological material with acyl chloride and thereafter copolymerizing the functionalized pharmacologic material with a monomer or a mixture of monomers in a radical polymerization process (col. 3, ll. 40-52). The method of Plate produces a composition which has "the advantage that [the pharmacologic materials] are not leached out and retain their pharmaceutical effectiveness for a long period of time." (Abstract)

The present claims are directed to pharmaceutical compositions and methods for their synthesis or use. Claim 5 (from which claims 6-12, and 17-21 depend) states:

> 5. A biomaterial formed from the cross-linking of two or more precursor components, wherein at least one of said precursor components has the formula:
>
> $D\text{-}Y\text{-}C(O)\text{-}(CH_2)_n\text{-}S\text{-}(CH_2)_2\text{-}CO\text{-}X\text{-}P$,
> $D\text{-}Y\text{-}C(O)\text{-}(CH_2)_n\text{-}NH\text{-}(CH_2)_2\text{-}CO\text{-}X\text{-}P$,

D-Y-C(O)-$(CH_2)_n$-NH-U-P,
D-Y-C(O)-$(CH_2)_n$-S-U-P,
D-Y-C(O)-$(CH_2)_2$-S-L-S-CH_2-CH_2-CO-X-P,
D-Y-C(O)-$(CH_2)_2$-S-L-S-U-P,
D-Y-C(O)-$(CH_2)_2$-NH-L-S-CH_2-CH_2-CO-X-P,
D-Y-C(O)-$(CH_2)_2$-NH-L-S-U-P,
D-Y-C(O)-$(CH_2)_2$-S-L-NH-CH_2-CH_2-CO-X-P,
D-Y-C(O)-$(CH_2)_2$-S-L-NH-U-P,
D-Y-C(O)-$(CH_2)_2$-NH-L-NH-CH_2-CH_2-CO-X-P, or
D-Y-C(O)-$(CH_2)_2$-NH-L-NH-U-P,

wherein D is a pharmaceutically active moiety; n is 1 or 2; Y is O, NH, or N; L is a linear or branched linker; X is O or N; P is a water-soluble polymer or a water-swellable polymer comprising one or more conjugated unsaturated groups; and U is the product of the addition of a nucleophile to an electrophilic group that is attached to said polymer.

The claim is thus directed to a cross-linked composition in which one of the precursors has a secondary amino or thioether group located α or β to an amide or ester bond onto a pharmaceutically active moiety. Plate does not teach or suggest a composition having these properties.

Plate does not teach the limitations of claim 5. Claim 5 requires a precursor molecule having a pharmaceutically active moiety bound to a polymer through an amide or ester group that is α or β to a secondary amine or a thioether. While Plate does teach pharmaceutically active moieties coupled by amide or ester bonds, these bonds are to linkers containing unsaturated groups (col. 14, ll. 34-55) and not α or β amino or thioether groups. Indeed, none of the reagents taught by Plate for the functionalization of pharmaceutically active moieties (col. 14, ll. 45-55) produces an α or β amino or thioether group, as required by claim 5. Since Plate does not teach the precursor of claim 5, the rejection of claim 5 for anticipation should be withdrawn.

Claim 33 (from which claim 34 depends) recites:

> 33. A pharmaceutically active compound of the formula D-O_2C-$(CH_2)_n$-SH or D-N(O)C-$(CH_2)_n$-SH, wherein n is 1 or 2 and D is a pharmaceutically active moiety.

The compositions of claim 33 contain a thiol[1] group located α or β to an amide or ester bond onto a pharmaceutically active moiety. Similar to the thioethers α or β to an amide or ester in claim 5, Plate fails to disclose a thiol α or β to an amide or ester, as recited in claim 33, and the § 102 rejection of claims 33 and 34 should therefore be withdrawn.

Claims 13, 14, 22-27, and 35-39 are directed to methods of forming a biomaterial of the invention. Each of these methods, as stated in independent claims 13, 35, and 37, requires the coupling of a pharmaceutically active compound to a polymer by a conjugate addition reaction. In contrast, Plate teaches covalently bonding a pharmacologic compound to a polymer by radical polymerization (col. 14, ll. 10-33). Radical polymerization occurs by a different mechanism than a conjugate addition reaction, and thus, Plate fails to teach the coupling of a pharmaceutically active compound to a polymer by a conjugate addition reaction, as recited in claims 13, 35, and 37. The rejection of claims 13, 14, 22-27, and 35-39 for anticipation should, therefore, be withdrawn.

Claim 15 (from which claims 16 and 28-32 depend) states:

> 15. A method of treating or preventing disease, disorder, or infection in a mammal by administering to said mammal a biomaterial comprising a pharmaceutically active moiety, wherein said biomaterial has an ester or

[1] Applicants note that the previous reply referred to the compounds of claim 33 as thioethers instead of thiols, and Applicants further note that the analysis in the previous reply is valid for both thiols and thioethers.

> amide bond onto said pharmaceutically active moiety, said bond having a half-life of between 1 hour and 1 year in an aqueous solution at pH 7.4 and 37 °C.

This claim is directed to a method for the controlled release of a pharmaceutically active moiety from a biomaterial (pg. 85, ll. 5-23). As the instant specification states:

> [T]he presence of a thioether near the ester or amide bond that attaches the pharmaceutically active compound to the linker enhanced the rate of hydrolysis of the bond, relative to a simple aliphatic ester or amide. Typically, a completely aliphatic ester is expected to have a half-life of hydrolysis in buffered water at pH 7.4, 37 °C on the order of years, because of the hydrophobicity of the aliphatic chain.... (pg. 89, ll. 18-24).

The specification further states that amine groups may also increase hydrolysis of an ester or amide bond. In contrast to the method of claim 15, Plate teaches:

> Generally, if it is desired that a pharmacologic effect of a particular material be retained for a long period of time (often indefinitely), such pharmacologic material would be chemically bound to the base polymer or copolymerized with other monomers. If it is desired that a pharmacologic material back out of the polymer over a limited period of time, it would be preferable to incorporate it physically with a polymer... (col. 4, ll. 14-25; emphasis added)

Plate thus teaches the physical, and not chemical, incorporation of a pharmacologic material into a polymer and not the release of a pharmaceutically active moiety by the hydrolysis of an amide or ester bond. Although Plate discloses the use of amide or ester bonds in the coupling of pharmacologic materials to a polymer, Plate is silent with regard to a rate of hydrolysis, and therefore, does not explicitly teach the limitations of claim 15. In addition, the examples of amide or ester bonds cited by Plate do not inherently have the desired rate of hydrolysis because, as taught by the Applicants, the rate of hydrolysis

depends on nearby functional groups. The rejection of claims 15, 16, and 28-32 for anticipation should be withdrawn.

Rejections under 35 U.S.C. § 103(a)

Claims 5-39 stand rejected for obviousness in view of Plate. M.P.E.P. § 2143 states:

> To establish a *prima facie* case of obviousness, ... there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings...[, and] the prior art reference... must teach or suggest all the claim limitations.

Applicants assert that this standard has not been met in the present case.

Regarding claims 5 and 33 (and their dependent claims), which are directed to compositions, as stated above, Plate does not teach or suggest all of the limitations of these claims. Claim 5 is directed to a material containing an amino or thioether group α or β to an ester or amide bond, and claim 33 is directed to a material containing a thiol group α or β to an ester or amide bond. These compounds have increased rates of hydrolysis compared to aliphatic esters or amides and thus, can be used in time-release formulations for drug delivery. As stated above, Plate teaches the coupling of pharmacologic materials to groups with unsaturated bonds for use in radical polymerization but does not teach or suggest amide or ester bonds having an α or β amino or thioether/thiol group. In addition, Plate teaches that for drug release "it would be preferable to incorporate [the drug] physically with a polymer..." (col. 4, ll. 20-21) which teaches away from the compositions of instant claim 5, which requires chemical

incorporation of a pharmaceutically active moiety. Since Plate does not teach or suggest the limitations of claims 5 and 33, the rejection of claims 5-12, 7-21, and 33-34 for obviousness should be withdrawn.

Regarding claims 13, 14, 22-27, and 35-39, which are directed to methods of forming biomaterials, again, Plate does not teach or suggest the claimed methods. The cited claims are directed to linking a pharmaceutically active compound to a polymer via a conjugate addition reaction. Plate only teaches the use of radical-based coupling chemistries and does not teach or suggest the limitations of the claims directed to methods of forming biomaterials. The rejection of claims 13, 14, 22-27, and 35-39 should, therefore, be withdrawn.

Claims 15, 16, and 28-32 are directed to a method of treating or preventing a medical condition by administering a composition that contains an amide or ester bond that has a half-life of between 1 hour and 1 year. Plate does not teach or suggest such a method. Indeed, Plate teaches away from the method of claim 15 because it teaches the physical rather than chemical incorporation of pharmacologic material into a polymer for release in vivo. In addition, Plate teaches that chemical bonding is a desirable route to *retain* a pharmacologic material in a polymer for a long period of time, which is the *opposite* result of the method of claim 15. Thus, the rejection for obviousness of claims 15, 16, and 22-28 should be withdrawn.

CONCLUSIONS

Applicants submit that the claims are in condition for allowance, and such action is respectfully requested. Enclosed is a petition to extend the period for reply for two months, to and including February 26, 2003. If there are any additional charges, or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: February 26, 2003

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Clean Copy of Pending Claims

5. (Twice Amended) A biomaterial formed from the cross-linking of two or more precursor components, wherein at least one of said precursor components has the formula:

D-Y-C(O)-$(CH_2)_n$-S-$(CH_2)_2$-CO-X-P,

D-Y-C(O)-$(CH_2)_n$-NH-$(CH_2)_2$-CO-X-P,

D-Y-C(O)-$(CH_2)_n$-NH-U-P,

D-Y-C(O)-$(CH_2)_n$-S-U-P,

D-Y-C(O)-$(CH_2)_2$-S-L-S-CH_2-CH_2-CO-X-P,

D-Y-C(O)-$(CH_2)_2$-S-L-S-U-P,

D-Y-C(O)-$(CH_2)_2$-NH-L-S-CH_2-CH_2-CO-X-P,

D-Y-C(O)-$(CH_2)_2$-NH-L-S-U-P,

D-Y-C(O)-$(CH_2)_2$-S-L-NH-CH_2-CH_2-CO-X-P,

D-Y-C(O)-$(CH_2)_2$-S-L-NH-U-P,

D-Y-C(O)-$(CH_2)_2$-NH-L-NH-CH_2-CH_2-CO-X-P, or

D-Y-C(O)-$(CH_2)_2$-NH-L-NH-U-P,

wherein D is a pharmaceutically active moiety; n is 1 or 2; Y is O, NH, or N; L is a linear or branched linker; X is O or N; P is a water-soluble polymer or a water-swellable polymer comprising one or more conjugated unsaturated groups; and U is the product of the addition of a nucleophile to an electrophilic group that is attached to said polymer.

6. The biomaterial of claim 5, wherein said cross-linking occurs in the presence of a polymer that does not contain a pharmaceutically active moiety, said polymer comprising two or more conjugated unsaturated groups, wherein said polymer is incorporated into said biomaterial.

7. (Amended) The biomaterial of claim 5, wherein said cross-linking occurs in the presence of a polymer comprising two or more nucleophilic groups.

8. The biomaterial of claim 5, wherein said water-soluble or water-swellable polymer is selected from the group consisting of poly(ethylene glycol), poly(ethylene oxide), poly(vinyl alcohol), poly(acrylic acid), poly(ethylene-co-vinyl alcohol), poly(vinyl pyrrolidone), poly(acrylic acid), poly(ethyloxazoline), poly(ethylene oxide)-co-poly(propylene oxide) block copolymers, or water-soluble or water-swellable copolymers comprising these polymers, and their derivatives comprising conjugated unsaturated groups.

9. The biomaterial of claim 5, wherein said unsaturated groups are not activated as to undergo nucleophilic substitution reactions.

10. (Amended) The biomaterial of claim 5, wherein said conjugated unsaturated groups are selected from the group consisting of acrylates, methacrylates, acrylamides, methacrylamides, acrylonitriles, and quinones.

11. (Amended) The biomaterial of claim 5, wherein said crosslinking occurs in the presence of a molecule comprising an adhesion site, growth factor binding site, protease binding site, or enzymatically degradable site, and further comprises at least one strong nucleophile or a conjugated unsaturated group.

12. (Amended) The biomaterial of claim 7, wherein said nucleophilic groups are selected from the group consisting of thiols and amines.

13. (Amended) A method of forming a biomaterial, said method comprising the steps of:

(a) attaching a pharmaceutically active compound to a linker molecule or incorporating a nucleophilic amine or thiol into a pharmaceutically active compound,

(b) removing any thiol- or amine-protecting groups in said linker,

(c) coupling a thiol, amine, or alkene group in said linker or incorporated into said pharmaceutically active compound to a water-soluble polymer or a water-swellable polymer comprising two or more conjugated unsaturated groups by a conjugate addition reaction to form a precursor component, and

(d) cross-linking the uncoupled conjugated unsaturated groups in one or more of said precursor components.

14. The method of claim 13, wherein said cross-linking of said uncoupled unsaturated groups occurs at or near a site within the body of a mammal.

15. (Amended) A method of treating or preventing a disease, disorder, or infection in a mammal by administering to said mammal a biomaterial comprising a pharmaceutically active moiety, wherein said biomaterial has an ester or amide bond onto said pharmaceutically active moiety, said bond having a half-life of between 1 hour and 1 year in an aqueous solution at pH 7.4 and 37 °C.

16. The method of claim 15, wherein said mammal is a human.

17. The biomaterial of claim 5, wherein said pharmaceutically active moiety is derived from one of the group consisting of synthetic organic molecules, naturally occurring organic molecules, nucleic acid molecules, biosynthetic proteins or peptides, naturally occurring peptides or proteins, and modified naturally occurring peptides or proteins.

18. The biomaterial of claim 5, wherein said pharmaceutically active moiety is paclitaxel, doxorubicin, 5-fluorodeoxyuridine, estradiol, 2-methoxyestradiol, or a derivative thereof.

19. The biomaterial of claim 5, wherein the half-life of the ester or amide bond onto said pharmaceutically active moiety is between 1 day and 9 months in an aqueous solution at pH 7.4 and 37 °C.

20. The biomaterial of claim 5, wherein the half-life of the ester or amide bond onto said pharmaceutically active moiety is between 2 days and 6 months in an aqueous solution at pH 7.4 and 37 °C.

21. The biomaterial of claim 5, wherein the half-life of the ester or amide bond onto said pharmaceutically active moiety is between 4 days and 3 weeks in an aqueous solution at pH 7.4 and 37 °C.

22. The method of claim 13, wherein said pharmaceutically active compound is derived from one of the group consisting of synthetic organic molecules, naturally occurring organic molecules, nucleic acid molecules, biosynthetic proteins or peptides, naturally occurring peptides or proteins, and modified naturally occurring peptides or proteins.

23. The method of claim 13, wherein said pharmaceutically active compound is paclitaxel, doxorubicin, 5-fluorodeoxyuridine, estradiol, 2-methoxyestradiol, or a derivative thereof.

24. The method of claim 13, wherein the precursor component includes an ester or amide bond with a half-life between 1 hour and 1 year in an aqueous solution at pH 7.4 and 37 °C.

25. The method of claim 13, wherein the precursor component includes an ester or amide bond with a half-life between 1 day and 9 months in an aqueous solution at pH 7.4 and 37 °C.

26. The method of claim 13, wherein the precursor component includes an ester or amide bond with a half-life between 2 days and 6 months in an aqueous solution at pH 7.4 and 37 °C.

27. The method of claim 13, wherein the precursor component includes an ester or amide bond with a half-life between 4 days and 3 weeks in an aqueous solution at pH 7.4 and 37 °C.

28. The method of claim 15, wherein said pharmaceutically active moiety is derived from one of the group consisting of synthetic organic molecules, naturally occurring organic molecules, nucleic acid molecules, biosynthetic proteins or peptides, naturally occurring peptides or proteins, and modified naturally occurring peptides or proteins.

29. The method of claim 15, wherein said pharmaceutically active moiety is paclitaxel, doxorubicin, 5-fluorodeoxyuridine, estradiol, 2-methoxyestradiol, or a derivative thereof.

30. The method of claim 15, wherein the bond has a half-life between 1 day and 9 months in an aqueous solution at pH 7.4 and 37 °C.

31. The method of claim 15, wherein the bond has a half-life between 2 days and 6 months in an aqueous solution at pH 7.4 and 37 °C.

32. The method of claim 15, wherein the bond has a half-life between 4 days and 3 weeks in an aqueous solution at pH 7.4 and 37 °C.

33. A pharmaceutically active compound of the formula $D\text{-}O_2C\text{-}(CH_2)_n\text{-}SH$ or $D\text{-}N(O)C\text{-}(CH_2)_n\text{-}SH$, wherein n is 1 or 2 and D is a pharmaceutically active moiety.

34. The pharmaceutically active compound of claim 33 further comprising at least one polymer cross-linked to the pharmaceutically active compound by a conjugated addition reaction between a thiol group of the pharmaceutically active compound and a conjugated unsaturated group of the polymer.

35. (Amended) A method of forming a biomaterial, said method comprising the steps of:

(a) attaching a pharmaceutically active compound to a linker molecule or incorporating a nucleophilic amine or thiol into a pharmaceutically active compound;

(b) coupling the thiol or amine in said linker or incorporated into said pharmaceutically active compound to a polymer comprising two or more conjugated unsaturated groups by a conjugate addition reaction to form a precursor component; and

(c) cross-linking the uncoupled conjugated unsaturated groups in one or more said precursor components.

36. The method of claim 35, wherein said cross-linking occurs at or near a site within the body of a mammal.

37. A method of forming a biomaterial, said method comprising the steps of:

(a) attaching a pharmaceutically active compound to a linker molecule or incorporating a nucleophilic amine or thiol into a pharmaceutically active compound;

(b) coupling the thiol or amine in said linker or incorporated into said pharmaceutically active compound to at least a first polymer comprising two or more conjugated unsaturated groups by a conjugate addition reaction to form a precursor component;

(c) providing at least a second precursor comprising nucleophilic groups; and

(d) cross-linking the conjugated unsaturated groups of the precursor of step b) to the nucleophilic groups of the precursor of step c) by a conjugated addition reaction.

38. The method of claim 37, wherein said cross-linking occurs at or near a site within the body of a mammal.

39. The method of claim 38, wherein said mammal is a human.

41. The method of claim 15, wherein said biomaterial is cross-linked.

42. (New) The method of claim 15, wherein said ester or amide bond is α or β to a secondary amine or a thioether.